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Nonparallel Changes in Global Left Ventricular Chamber Volume and Muscle Mass During the First Year After Transmural Myocardial Infarction in Humans

JOHN A. RUMBERGER, PHD, MD, FACC, THOMAS BEHRENBECK, MD, PHD,
JEROME R. BREEN, MD, JUDD E. REED, BS, BERNARD J. GERSH, MB, CHB, DPHIL, FACC
Rochester, Minnesota

Objectives. This study was designed to serially assess time-dependent changes in both chamber volume and myocardial muscle mass after infarction in humans.

Background. Dilation of the left ventricular chamber has been previously described after transmural myocardial infarction.

Methods. Global left ventricular chamber volumes and muscle mass were quantified by using cine computed tomographic scanning in 18 patients at hospital discharge and 6 weeks, 6 months and 1 year after an initial transmural myocardial infarction (12 anterior and 6 inferior). No patient had heart failure during the initial hospital stay or on any subsequent follow-up visit.

Results. The patients with anterior myocardial infarction (estimated infarct extent 27 ± 2% of left ventricle) demonstrated a progressive increase in left ventricular end-diastolic volume from 148 ± 9 ml (mean ± SEM) at hospital discharge to 180 ± 9 ml at 1 year after infarction ($p < 0.001$). However, global left ventricular muscle mass decreased significantly during the 1st 6 weeks after infarction but returned by 1 year to nearly the value determined at hospital discharge (177 ± 13 vs. 165 ± 10 g, p = NS). The changes in global muscle mass did not parallel the steady and progressive increases in chamber end-diastolic volume. The end-diastolic chamber volume to muscle mass ratio, an index of global left ventricular wall tension, increased steadily after hospital discharge but remained level by 1 year after infarction. The time course of changes in global end-systolic chamber volume was roughly proportional to the concomitant changes in end-diastolic volume. During this same time period, left ventricular stroke volume remained constant or improved from that determined at baseline. Global left ventricular end-diastolic and end-systolic volumes remained relatively static during the 1st year in the patient subgroup with inferior wall myocardial infarction (estimated infarct extent 10 ± 1% of left ventricle), but global muscle (myocardial) mass initially decreased and then increased in a pattern similar, although of smaller magnitude, to that observed in patients with anterior wall myocardial infarction.

Conclusions. Overall, left ventricular end-diastolic and end-systolic chamber volumes increase progressively from hospital discharge to 1 year after an initial transmural myocardial infarction in patients with a moderately large anterior wall infarction but remain stable in patients with a small inferior wall infarction. Concurrently, total left ventricular muscle mass decreases significantly during the initial 6 weeks after infarction (presumed largely secondary to changes in the necrotic segments) but then returns to the hospital discharge baseline values by 1 year. These data are consistent with the late development of, at most, limited ventricular hypertrophy in the noninfarcted myocardium that occurs well after the early and progressive left ventricular chamber dilation observed in patients with a moderate to large myocardial infarction. These data, in particular as applied to patients with anterior infarction, suggest that ventricular wall tension is significantly elevated at least during the 1st year after an initial transmural myocardial infarction. These observations may explain the potential utility of agents aimed at reducing afterload or ventricular wall tension during the early convalescent phase after myocardial infarction.

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The development of left ventricular chamber dilation after transmural myocardial infarction has been well documented at autopsy (1,2), in animals models (3–5) and in living patients (6–9) and is part of the spectrum of postinfarction left ventricular remodeling. However, the majority of studies have concentrated on detailing changes in global left ventricular chamber volumes or expansion both within and outside the infarct region, or both. Although it has been suggested in rat models of anterior wall myocardial infarction (10–12) that left ventricular hypertrophy develops in parallel with changes in chamber volumes, no data relating serial changes in both left ventricular chamber volumes and muscle mass have been previously reported in humans.

From the Departments of Cardiovascular Diseases and Internal Medicine and *Diagnostic Radiology, Mayo Clinic, Rochester, Minnesota. Dr. Rumberger is supported by an Established Investigator Award from the American Heart Association, Dallas, Texas; Grant 34508 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and the Mayo Foundation, Rochester. This study was presented in part at the 64th Annual Scientific Sessions of the American Heart Association, Anaheim, California, November 1991.

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Address for correspondence: John A. Rumberger, PhD, MD, Department of Cardiovascular Diseases and Internal Medicine, Mayo Clinic and Foundation, 200 First Street SW, Rochester, Minnesota 55905.

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Temporal and serial changes in left ventricular chamber volumes and left ventricular muscle mass in humans after acute myocardial infarction have important clinical implications. The absolute magnitude of left ventricular end-diastolic and end-systolic volumes after myocardial infarction has been demonstrated (13,14) to be better than global ejection fraction as a predictor of morbidity and mortality. Widespread recognition of these concepts has been the stimulus for several studies aimed at modifying left ventricular dilation after infarction by use of angiotensin-converting enzyme therapy (15), intravenous nitroglycerin (16,17) or other agents (18).

The concept of using the ratio of left ventricular end-diastolic chamber volume and muscle mass as an index of overall ventricular wall tension was first proposed by Gaasch (19) to describe adaptive responses of the ventricle to volume overload. Although much has been written about the detrimental effects of left ventricular hypertrophy on the myocardium in general (20) and in particular after myocardial infarction (2,12,21), initially its development in the presence of ventricular chamber dilation should be viewed as a proper adaptive response to an applied hemodynamic load. If the concepts put forward by Gaasch can be applied to the volume overload of ventricular remodeling, it would be expected that nearly parallel changes in left ventricular chamber volumes and muscle mass should occur after myocardial infarction to allow for normalization of global ventricular wall tension. Thus, in the presence of volume overload, as is the case with postinfarction remodeling, the overall development of left ventricular hypertrophy in the setting of ventricular chamber enlargement should be anticipated. Indeed, the lack of development of global left ventricular hypertrophy in the presence of significant chamber dilation after infarction may suggest a maladaptive mechanism. However, the time course of these features in patients after infarction has not been previously explored.

Our investigations regarding ventricular remodeling were initiated to serially investigate the adaptive responses of the human left ventricle to an initial transmural myocardial infarction. To examine details of the left ventricle, we used cine computed tomography, which has been extensively validated by our laboratory and others for quantitative measurements of left ventricular muscle mass (22,23), chamber volumes (24,25) and systolic (26,27) and diastolic (28,29) mechanics in humans.

Methods

Patient selection and entry criteria. Male and female patients hospitalized in the coronary care unit at the Mayo Clinic were identified within 1 to 3 days of an acute anterior or inferior wall myocardial infarction as possible candidates for study. Entry criteria were as follows: normal sinus rhythm, documentation to support the clinical diagnosis of acute transmural myocardial infarction (ST segment elevation ≥2 mm above baseline in at least two contiguous electrocardiographic [ECG] leads or development of new abnormal Q waves on the ECG [anterior precordial leads for anterior infarction, inferior limb leads for inferior infarction], or both), recent history of angina lasting >30 min, serial changes in creatine kinase and creatine kinase-MB isoenzymes consistent with acute myocardial infarction and age between 19 and 79 years. Exclusion criteria were documented or historical evidence of previous myocardial infarction (transmural or nontransmural), historical or physical examination findings consistent with left-sided valvular stenosis or regurgitation beyond grade I (the majority of patients had two-dimensional echocardiographic/Doppler examinations that confirmed these criteria), uncontrolled hypertension or cardiogenic shock or need for inotropic support. Concomitant therapy with nitrates, beta-adrenergic blocking drugs and/or calcium channel antagonists was not considered to be an exclusion criterion. Because all patients were to undergo contrast-enhanced cine computed tomographic examinations, the patient must have had no allergy to iodinated contrast medium and have a serum creatinine <1.6 g/dl. Finally, for entry into the protocol, the patient must have had the ability to undergo the initial cine computed tomographic examination within the 1st 10 days after acute myocardial infarction.

Before entry into the research protocol, each patient signed an informed consent for serial cine computed tomographic studies and underwent a physical examination conducted by one of the investigators.

Cine computed tomographic scanner and imaging protocols. The intent of the investigations was to examine quantitative left ventricular anatomy and function on a serial basis in patients after myocardial infarction. Although no imaging modality is totally without its limitations, cine computed tomography (also called ultrafast computed tomography, Imatron C-100) provides noninvasive, high quality temporal, spatial and density resolution images at multiple tomographic cardiac imaging planes using extensively validated methods of cardiac border definition (22–29).

The design and operation of the cine computed tomographic scanner has been described elsewhere (30) and does not require repetition here. For each study, prospective ECG triggering at the R wave (end-diastole) allowed for serial acquisition of polytomographic images of the heart at a rate of 17 frames/s. The relative and absolute timing for each image from the trigger signal as well as an analog of the surface ECG were recorded on the file header during each acquisition. Each tomographic level was 0.8 cm thick with a center to center distance between levels of 1 cm. Also recorded on the file header was the relative position of each scan with respect to the others in three-dimensional space. This facilitated quantification of left ventricular volumes and muscle mass.

Imaging of each subject was performed in a manner similar to that previously described (26,27,30). No premedications were given and the subject was instructed to fast and discontinue medications for ≥4 h before the study. Self-

adhering electrode pads were placed on the chest to allow for continuous ECG monitoring and as a trigger signal to the scanner. After placement of an 18-gauge, 5.08-cm catheter in a right antecubital vein, each subject was positioned in the scanner so as to acquire parallel tomographic images in the short axis (transverse cardiac) from the left ventricular apex through the base of the right ventricular outflow tract (31). A noncontrast localization scan was initially performed to determine the level of the left ventricular apex. The subject was then mechanically adjusted within the scanner gantry to ensure that the most caudad tomographic images were obtained at the level of the cardiac apex. This procedure assured that all subjects would be imaged in a uniform manner on the initial and follow-up scans.

Once the patient was positioned, an estimation of circulation time was determined during normal respiration after administration of a bolus injection of 10 ml of a dilute solution of magnesium sulfate (0.2%) (30) through the intravenous site. Noting the time between injection and the associated warm sensation under the tongue by the patient expedited accurate timing of the contrast injection and scanning sequences. During imaging, a powered injector delivered an infusion of nonionic contrast medium (Iohexol-350, Sterling Winthrop or Iopamidol-370, E.R. Squibb & Sons) through the intravenous catheter at 3 ml/s for 20 s. Starting image acquisition at the "circulation time" assured excellent and simultaneous opacification of both the left and right ventricular cavities at all levels scanned. Imaging initiated at the ECG R wave consisted of 13 consecutive frames through the cardiac cycle at six contiguous parallel tomographic levels. After a 2- to 5-min interval, the scanning table was moved (with the patient lying still) 6 cm and the scanning sequence and contrast injection repeated. The normal human left ventricle is roughly 10 to 12 cm from the tip of the epicardial apex, through the origin of the aortic root, just caudad to the level of the pulmonary valve. Most subjects (83%) entered into this protocol could be imaged in 12 ventricular levels; however, 3 patients (11%) had significant ventricular dilation and required a third scanning run constituting 18 tomographic levels of the heart. The total iodinated contrast load/patient for each scan in the series was approximately 1.2 ml/kg.

All data were stored on an optical disk for viewing and analysis on the Physician Analysis and Display console or directly on a SUN microcomputer workstation, using software developed in our laboratory (32). Once the raw image data were analyzed, numeric results were recorded directly into a relational data base.

Patients were scanned four times: at hospital discharge and at 6 weeks, 6 months and 1 year after myocardial infarction.

Determination of left ventricular chamber volume and muscle mass. Data were analyzed at each left ventricular tomographic level in an identical fashion for all patients at each of the four cine computed tomographic studies. First, the end-diastolic (image temporally related to the R wave on the ECG) and end-systolic (smallest chamber volume during the cardiac cycle) scans were identified at each tomographic level (24,26,27). Second, the areas inscribing the endocardial and epicardial surfaces of the left ventricle were determined using previously published criteria for accurate border definition using cine computed tomography (22). Tomographic ventricular chamber area was determined as the area inscribed by the endocardial surface and ventricular muscle (that is, myocardial) area; the latter was determined as the area inscribed between the endocardial and epicardial left ventricular surfaces, as previously described (24,26,27). For each ventricle, images were analyzed from the left ventricular apex through the basal tomographic sections, including the left ventricular outflow tract. Thus, there were 8 to 12 separate tomographic slices per study, depending on the overall long-axis dimensions of the left ventricle. Tomographic chamber volumes were the product of tomographic area (end-diastolic or end-systolic) and slice thickness. Tomographic left ventricular muscle mass was the product of muscle (myocardial) area, slice thickness and the specific gravity of myocardium. Although it was appreciated that the specific gravity of functional myocardium and infarcted myocardium are not identical, a single value was chosen for convenience to represent all myocardial surfaces (1.05 g/ml). Global (or total) left ventricular chamber volumes were determined by summing the tomographic chamber (end-diastolic and end-systolic) volumes and tomographic muscle (end-diastolic) masses over all slices (modified Simpson's rule) from apex to base (22,24–27).

Estimation of extent of myocardial infarction. To provide an estimate of the overall effect of infarct extent on chamber volumes and left ventricular muscle mass, an index of myocardial damage was developed from quantitative analysis of regional chamber motion on the scan performed at hospital discharge. Exact quantification of left ventricular myocardial infarct size in humans with tomographic imaging techniques can be problematic, especially when using information related to analysis of regional wall motion abnormalities (33). However, it was reasoned that a consistent application to defining an index of infarct size at hospital discharge would be acceptable for longitudinal comparison studies performed in the same group of patients.

Previous studies using cine computed tomography to define ejection fraction within regions of the tomographic plane in normal patients demonstrated a fair degree of heterogeneity of these values with use of either a floating point endocardial or floating point epicardial centroid method (26). Studies using two-dimensional echocardiography to evaluate the extent of regional wall motion abnormalities after myocardial infarction have used both centroid methods; however, Zoghbi et al. (34) have shown that accurate definition and quantification of regional wall motion abnormalities to define infarct extent can be approximated using a floating point epicardial centroid method.

Analysis of the formerly cited cine computed tomographic study in normal patients (26), which used the epicar-

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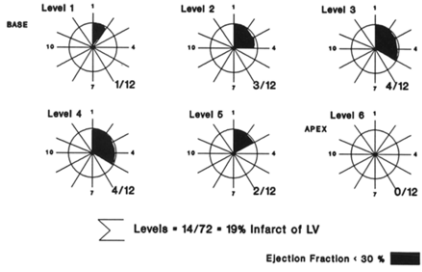


Figure 1. Estimation of index of infarct size—example at six tomographic levels. Schematic illustration of the method used to estimate infarct extent from discharge cine computed tomographic examinations. The darkened areas represent sections of the tomographic image where the regional ejection fraction was <30%. Twelve regions were examined at each tomographic level using an epicardial floating point centroid method. See text for details. LV = left ventricle.

dial centroid method, demonstrated that the average regional ejection fraction of the human left ventricle was approximately 65 ± 6% and no regional ejection fraction at any level was <30%. For the purposes of the current investigation, identification of both the endocardial and epicardial surfaces was done on the end-diastolic and end-systolic images; thereafter, each set of tomographic images was divided by computer into 12 pie-wedged (22.5°) segments and the regional ejection fraction was determined using a floating point epicardial centroid as the reference. Any regional ejection fraction <30% that represented a value >2 SD from the normal mean value was considered to be within a region of infarction. Thus, the areas with abnormal regional ejection fraction represented areas of severe hypokinesia or akinesia. The total number of segments with severe hypokinesia or akinesia of the 12 regional segments examined was determined in each left ventricular tomographic level. The sum of regional tomographic segments with severe hypokinesia or akinesia on the cine computed tomographic scan performed at hospital discharge was expressed as a percent of the total number of segments/heart examined and was designated as the index of initial infarct size. An example of this calculation is shown schematically in Figure 1.

Statistics. Data are presented as mean value ± SEM. Statistical comparisons between left ventricular chamber volumes, muscle mass, ejection fraction, heart rate and mean arterial pressure at each cine computed tomographic scan visit were determined by using a repeated measures analysis of variance (ANOVA) with a Student-Newman-Keuls *t* test for comparisons between visits. A p value < 0.05 was considered to achieve statistical significance.

Results

Patient demographics. Results are presented from a total of 18 patients who completed four successful scans during the 1st year after myocardial infarction. Twelve had anterior and six had inferior wall myocardial infarction. Interventions at the time of presentation for acute myocardial infarction included urgent coronary angioplasty (eight anterior vs. two inferior), intravenous thrombolytic therapy (three anterior vs. one inferior) and conventional therapy without attempts to establish acute reperfusion (one anterior vs. three inferior). As directed by their respective cardiologists, all but one patient had selective coronary angiography performed urgently or electively within 1 week of acute myocardial infarction; of these patients, all had a patent infarct-related coronary artery documented at the end of angiography either as a result of early or late thrombolysis or direct coronary angioplasty, or both.

No patient had clinical symptoms consistent with heart failure at the time of presentation to the hospital, at the initial cine computed tomographic scan or at the time of a subsequent scan visit. Initial cine computed tomographic scanning was performed within 8 ± 1 days; after myocardial infarction follow-up scans were performed at 61 ± 3, 213 ± 8 and 398 ± 7 days after infarction. For purposes of discussion, these scan dates are referred to as hospital discharge, 6 weeks, 6 months and 1 year, respectively. Patients ranged in age from 42 to 72 years (average 57 ± 3). There were 3 women and 15 men.

The majority of patients in both the anterior and the inferior infarction subgroups were taking a beta-blocker and long-acting nitrates at all four scan visits (11 and 9, respectively, for anterior infarction and 6 and 6, respectively, for inferior infarction). The concomitant use of calcium channel blockers was limited (4 vs. 0 anterior vs. inferior infarction). One patient in the inferior infarction group was taking an angiotensin-converting enzyme inhibitor (lisinopril) for therapy of hypertension. None of the patients with anterior infarction were taking angiotensin-converting enzyme inhibitors at any time during the study period. No patients were prescribed diuretic drug or digitalis preparations at any time during the 1-year study.

Indexes of the initial myocardial infarct extent were 27 ± 2% of the left ventricle for anterior wall infarction and 10 ± 1% of the left ventricle for inferior wall infarction. These values for initial infarct extent are consistent with estimates made in prior studies done at the Mayo Clinic (36) using technetium-99m sestamibi in survivors of anterior and infe-

Table 1. Hemodynamic Data in the Study Patients at the Time of Cine Computed Tomographic (CT) Scans Performed at Hospital Discharge and During Follow-Up After an Initial Transmural Myocardial Infarction

Cine CT Scanning Dates	Heart Rate (beats/min)	Mean Arterial Pressure (mm Hg)	LV Ejection Fraction	LV Stroke Volume (ml)
	Anterior Wall Myocardial Infarction (n = 12)			
Discharge	71 ± 2	82 ± 2	50 ± 2	74 ± 5
6 Weeks	69 ± 2	83 ± 3	54 ± 2	89 ± 5*
6 Months	66 ± 2	89 ± 4	53 ± 2	89 ± 6*
1 Year	64 ± 3*	99 ± 4*	52 ± 3	93 ± 6*
	Inferior Wall Myocardial Infarction (n = 6)			
Discharge	67 ± 4	85 ± 2	54 ± 2	73 ± 7
6 Weeks	59 ± 4	87 ± 5	57 ± 1	76 ± 6
6 Months	61 ± 3	87 ± 4	61 ± 4	87 ± 9
1 Year	60 ± 4	88 ± 6	60 ± 1	77 ± 5

*$p < 0.05$ versus discharge cine computed tomographic scan data. Data are reported as mean ± SEM. LV = left ventricular.

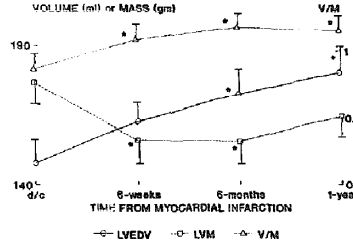


Figure 2. Left ventricular end-diastolic chamber volume (LVEDV), myocardial muscle mass (LVM) and their ratio (V/M) during the 1st year after anterior wall myocardial infarction (n = 12). Data are presented as mean value ± SEM. See text for details. *$p < 0.05$ versus hospital discharge (d/c).

rior wall myocardial infarction. No patient required repeat coronary angioplasty, underwent coronary artery bypass grafting or had a documented recurrent myocardial infarction during the 1-year study and follow-up period.

Patients remained in normal sinus rhythm at all times throughout the study period. Heart rate, mean arterial pressure (estimated from cuff measurements), global left ventricular ejection fraction and global stroke volume for all patients for each of the four cine computed tomographic scan dates are presented in Table 1. There were no statistically significant changes in global ejection fraction during this initial year after infarction for either patient subgroup. However, global stroke volume was greater at all subsequent visits compared with the value at hospital discharge in the patients with anterior infarction. There were no significant changes in stroke volume during the initial year after infarction in the subgroup with inferior infarction. Likewise, heart rate and mean arterial pressure remained unchanged in this patient subgroup; however, heart rate was significantly lower and arterial pressure significantly higher at 1 year compared with baseline hospital discharge values in the subgroup with anterior wall myocardial infarction.

Anterior wall myocardial infarction. In the patient subgroup with acute anterior wall myocardial infarction, left ventricular global end-diastolic volume increased by 22% from 148 ± 9 ml at hospital discharge to 180 ± 9 ml at 1 year ($p < 0.001$). The left ventricular end-diastolic muscle mass was 177 ± 13 g at hospital discharge and 165 ± 10 g at 1 year (p = NS). Thus, at first review, left ventricular muscle mass appeared to remain static at a time when there was a significant increase in left ventricular end-diastolic chamber volume.

Figure 2 graphically demonstrates the time course of serial changes in left ventricular chamber volume and muscle mass as assessed by cine computed tomography. The volume/mass ratio here represents the ratio of global end-diastolic chamber volume to global end-diastolic muscle mass. As shown, the left ventricular end-diastolic chamber volume in these patients with anterior wall myocardial infarction progressively increased during the initial year after infarction. However, the left ventricular muscle mass decreased significantly during the 1st 6 weeks but returned to baseline values by 1 year after infarction. The volume/mass ratio increased progressively during the 1st year consistent with the nonparallel changes in chamber volume and muscle mass but appeared to stay level by 1 year. Normal values for volume/mass ratio are on the order of ≤0.9.

Inferior wall myocardial infarction. In contrast to the patients with anterior wall myocardial infarction, patients with inferior wall necrosis had little or no change in left ventricular end-diastolic chamber volume during the 1st year. The value for this variable at hospital discharge was virtually identical to the value at 1 year (136 ± 5 ml for each). However, the time course of serial changes in global left ventricular myocardial muscle mass during the year after infarction closely resembled that observed in the patients with anterior wall infarction (Fig. 2) albeit at a lower magnitude. Figure 3 shows results from the patients with inferior wall infarction.

Left ventricular end-systolic volumes. Figure 4 shows the time course of changes in left ventricular end-systolic volumes during the 1st year after transmural infarction for both the anterior and inferior infarction subgroups. For patients with inferior infarction, no significant change was noted during the 1-year study period. In contrast, in patients with anterior wall myocardial infarction, end-systolic volume progressively increased during the year after infarction, increasing significantly by approximately 20% from the baseline value at hospital discharge of 74 ± 6 to 89 ± 7 ml at 1-year. The majority of this increase was noted after 6 weeks.

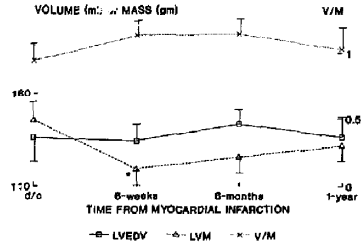
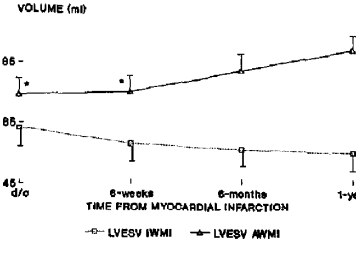


Figure 3. Left ventricular end-diastolic chamber volume (LVEDV), myocardial muscle mass (LVM) and their ratio (V/M) during the 1st year after inferior wall myocardial infarction (n = 6). Data are presented as mean value ± SEM. See text for details. *p < 0.05 versus hospital discharge (d/c).

Discussion

During the year after an initial transmural myocardial infarction, the results from this study demonstrate that global left ventricular end-diastolic and end-systolic chamber volumes increase progressively from the time of hospital discharge in patients with a moderately large anterior wall myocardial infarction but tend to remain stable in patients with a small inferior wall infarction. To a great extent, these differences are most likely a reflection of the overall magnitude of the initial wall motion abnormalities (that is, index of infarct extent), as has been shown previously (9) (however, the results do not rule out a separate effect related to infarct site, such as buttressing by the diaphragm in inferior infarction, thus potentially limiting infarct expansion). An analysis of any independent effect of the "open artery" on limiting chamber dilation after infarction is nullified in this study by the fact that all but one patient had documentation of an open artery at hospital discharge. However, regardless of the extent of left ventricular chamber remodeling after infarction, ejection fraction, as the ratio of stroke volume to end-diastolic volume, remained unchanged during the 1st year in both infarction subgroups, largely reflecting parallel changes in both stroke volume and end-diastolic volume after infarction (Table 1, Fig. 1). This observation emphasizes the limited value of serial assessments of global left ventricular ejection fraction to define the consequences of postinfarction left ventricular remodeling in humans.

Figure 4. Left ventricular end-systolic chamber volume (LVESV) during the 1st year after anterior (AWMI) and inferior (IWMI) wall myocardial infarction. Data are presented as mean value ± SEM. See text for details. *p < 0.05 versus 1 year. d/c = hospital discharge.



During this same time period, there were dynamic changes in global left ventricular muscle mass in patients with both anterior and inferior wall infarction; these changes did not parallel the time course of concomitant changes in end-diastolic or end-systolic chamber volume. Total left ventricular muscle mass initially decreased during the 1st 6 weeks after infarction but then showed a trend toward an increase thereafter, returning by 1 year to nearly the value determined at hospital discharge. If this late return of global left ventricular muscle mass to baseline values, especially in the subgroup with anterior infarction, reflected the development of ventricular hypertrophy in the noninfarct region, its magnitude was small and occurred with a significant time lag or delay in relation to the early and progressive increases in left ventricular chamber volumes.

Finally, the left ventricular chamber volume to muscle mass ratio, as an index of long-term changes in left ventricular wall tension at rest, progressively increased at least during the 1st 6 months after myocardial infarction. Thereafter, with the suggestion of a positive trend in global left ventricular muscle mass at 1 year, it tended to stay level. In patients with anterior wall infarction, however, the plateau value for volume/mass ratio was significantly increased above normal.

Postinfarction left ventricular remodeling. This is the first study to employ the quantitative attributes of cine computed tomographic scanning to define the nature and extent of postinfarction left ventricular remodeling in humans. The changes reported in left ventricular chamber volumes from early (hospital discharge) to late (≥1 year) after transmural myocardial infarction are consistent with what has been noted by other laboratories. However, the unique feature here is the quantification of serial changes in both left ventricular chamber volumes and muscle mass over the 1st 12-month period after documented transmural myocardial infarction.

Previous studies in animals and patients have shown that left ventricular remodeling begins within minutes to hours after myocardial infarction. By the time of the initial cine computed tomographic study at a mean of 8 days after infarction, ventricular dilation surely was evident in the patients examined. In fact, the value of 148 ± 9 ml for end-diastolic volume in the patients with anterior infarction was above that determined by cine computed tomography in

a group of 11 normal men (133 ± 10 ml) (26). In contrast, however, although at present we have no data on left ventricular chamber volume and muscle mass beyond 1 year, the general trend demonstrated in Figure 2 suggests that chamber dilation may not be completed by 1 year in the group with a moderately large anterior wall infarction.

These observations may have significant clinical implications. Data from the Framingham Heart Study (36) have shown a 23% incidence of clinical heart failure by 10 years after myocardial infarction. Although interpretation of these data in the modern era must be done in view of current trends toward aggressive therapy for known risk factors for heart failure (such as hypertension and early attempts to limit infarct size by thrombolytic agents and coronary angioplasty), we believe that remote myocardial infarction with progressive left ventricular chamber dilation accompanied by nonparallel changes in left ventricular muscle mass may be one of the most common causes for the eventual development of congestive heart failure.

White et al. (14) have clearly demonstrated the importance of left ventricular end-systolic volume as a prognostic factor after myocardial infarction. Our studies demonstrated that end-systolic volume increased during the year after anterior wall myocardial infarction nearly in parallel with the increases in left ventricular end-diastolic volume. The similar changes in stroke volume and end-diastolic volume during the year after infarction were factors leading to the lack of change in left ventricular ejection fraction during the examination period in both patient subgroups. Potential mechanisms to explain the continued necessity for progressive chamber dilation during the 1st year after a moderately large anterior infarction are probably multifactorial and include factors not measured in the current study; however, the increases in stroke volume concomitant with increases in end-diastolic volume suggest a Frank-Starling mechanism. Progressive elevation in wall tension as reported here in the weeks and months after myocardial infarction, as either cause or effect, undoubtedly contributed to the pattern of postinfarction remodeling. Recent results from the placebo arm of the Studies of Left Ventricular Dysfunction (SOLVD) Trial (37) indicate that neurohumoral axis activation and relative serum catecholamine excess can be seen in individuals with only a mild reduction in ejection fraction and in the absence of clinical congestive heart failure. The normal regulatory feedback mechanisms appear to be improperly set in the presence of mild to moderate cardiac dysfunction, even in the presence of normal stroke volume and heart rate (as was the case in our patient subgroups). Continued investigations into the pathophysiology of left ventricular remodeling after transmural infarction are warranted and could be crucial to developing an understanding of the effect of therapeutic interventions aimed at reducing asymptomatic ventricular remodeling or its long-term consequences, or both.

The time course of serial changes in left ventricular muscle mass during the 1st year after infarction in humans has not been examined previously. The significant reduction in global left ventricular muscle mass during the first 6 weeks after infarction was initially unanticipated. However, it has been established that during this time period the necrotic region becomes a fibrous firm scar, with myocyte "dissolution" and loss of edema in the infarct and peri-infarct regions.

To illustrate the potential magnitude to which myocyte dissolution and other factors may contribute to an initial loss of total myocardial muscle mass during the first 6 weeks after infarction, consider the data from the patients with anterior infarction. The mean left ventricular muscle mass was 177 g at hospital discharge (Fig. 2). In this patient subgroup, the mean infarct size was on the order of 25% of the left ventricle. Thus, given the assumptions inherent in our definition of infarction and by implication the extent of necrosis, on the average, 44 g of the myocardium was damaged. If we consider or assume that the mass of infarcted myocardium after architectural reparative changes in the necrotic area because of myocyte dissolution and other factors (for example, loss of intramyocardial blood volume) was reduced by 50% during the 6 week recovery period (38), the overall reduction in global left ventricular muscle mass would be on the order of 22 g. The actual left ventricular muscle mass at 6 weeks in this patient group was 156 g, a 21 g difference from that determined at hospital discharge. A similar estimation can be made for the smaller but statistically significant changes in myocardial muscle mass observed during the first 6 weeks after infarction in the patients with inferior wall necrosis (Fig. 3).

Calculations made using cine computed tomography on the myocardium represent muscle volume, not muscle mass; the specific gravity was assumed for uniformity of presentation and was not measured. In the normal situation, myocytes constitute ≥90% of the total left ventricular muscle volume, the remainder consisting of intramyocardial blood volume, interstitial material and other cells (such as inflammatory cells) known to be present in the acutely necrotic areas. However, by 6 weeks after infarction, the changes in the infarct region are complete or nearly complete (39) and any subsequent changes in left ventricular muscle volume should, for the most part, be reflective of changes in myocyte volume (or muscle mass) in the remaining normal myocardium. A recent publication by Mitchell et al. (40) has shown that little or no change in infarct segment length (a necessary factor for "infarct expansion") occurs after approximately 3 weeks after acute myocardial infarction. The general trend seen in both infarction subgroups for left ventricular myocardial volume (or mass) to return to baseline values by 1 year is consistent with a slow and limited development of left ventricular hypertrophy in the noninfarcted myocardium.

These observations are not inconsistent with prior studies (10, 12) in the rat with anterior infarction, in which cellular hypertrophy was noted relatively early after infarction in the noninfarcted region. However, the current data suggest that

the predominant change in global (that is, total) left ventricular myocardial mass is one of reduction during the 1st 6 weeks after infarction and one of slow return to baseline values thereafter. The absence of any dramatic change in global left ventricular muscle mass during the period of 6 weeks to 6 months after infarction suggests that any hypertrophy in the noninfarcted region during the 1st 6 weeks in humans may be significantly limited or even absent. In fact, despite increases in ventricular chamber volume after anterior infarction, global left ventricular muscle mass at 1 year was in the range of normal values as determined by cine computed tomography (26).

The left ventricular chamber volume to left ventricular muscle mass ratio has been popularized by Gaasch (19) and others as indexes of the response of the heart to volume overload. The chamber dilation observed after myocardial infarction may be viewed as a volume overload situation. The observations reported here indicate that changes in global left ventricular muscle mass do not parallel or lag significantly behind progressive global chamber dilation after myocardial infarction. By 1 year after infarction, the volume/mass ratio still remains significantly above normal. The long-term implications of these observations remains to be determined, but the presumed long-term elevation in left ventricular wall tension may play an important role in the observed progression of remodeling, at least in patients with a moderately large anterior wall myocardial infarction. The contribution or interaction of abnormal regulatory neurohormone levels and elevated wall tension to progressive ventricular dilation after infarction requires further study. Data continue to amass regarding salutary roles for the long-term use of angiotensin-converting enzyme inhibitors (5,15,41); additionally, the early use of intravenous nitroglycerin (16,17) may provide long-term effects on limiting chamber dilation after myocardial infarction. Both of these agents may have potent effects on limiting increases in global wall tension or the disparity between regional wall tensions after infarction, or both.

Limitations of the study. Determinations of left ventricular volumes by cine computed tomography are known to be among the most accurate possible in any experimental study group. Recent studies (22,23) have been published regarding the quantitative accuracy and reproducibility of measurements of left ventricular muscle mass in animals and humans using cine computed tomography. Overall accuracy in animals has shown an SEE of 4 to 6 g (or ≈5%). Likewise, quantitative determinations of cardiac volumes have been demonstrated in animals and humans. Errors are ≈<5% for calculations of global stroke volumes of both the left and right ventricles (24,25,27). Thus, no significant errors in serial definition of left ventricular chamber volumes and muscle mass that could influence the results of the current investigation are considered.

One concern that is common to human studies, where exacting controls of experimental conditions are difficult, is the influence of variable preload and afterload on individual measurements of left ventricular chamber volumes (such an effect, however, should not significantly alter the quantification of left ventricular muscle mass). At all times, the patient hemodynamic values noted in Table 1 remained within the expected norms for a random group of adults, but the heart rate and mean arterial pressure were different at the end compared with the beginning of the study in the subgroup with anterior wall infarction. This subgroup also had the most dramatic changes in chamber volume and myocardial muscle mass during the 1st year after infarction. The magnitude of these slight differences between loading conditions on ventricular mechanics would be difficult to predict but could conceivably account for some of the observed increases in ventricular chamber volumes noted during the 1 year follow-up period; however such minimal differences would not be expected to fully explain the patterns noted in Figures 2 and 4. Trends for time-dependent changes in chamber volume and muscle mass noted at 1 year after infarction were consistent with the findings at 6 months and 6 weeks after infarction. Within the understandable constraints of interpretation related to variable loading conditions, we contend that the measured patterns of changes in left ventricular volumes are a direct physiologic consequences of postinfarction ventricular remodeling.

Beyond the known effect early during the course of acute myocardial infarction, the use of beta-blockers has been shown to have little or no effect on the magnitude of postinfarction remodeling (18). Patients who began beta-blocker therapy at or about the time of hospital discharge continued this therapy throughout the 1-year period. Short-term (and possibly long-term) nitrate therapy, in contrast, may play a role (16,17); however, this class of medication was taken by the majority of patients in the study throughout the examination period. In our institution, intravenous nitroglycerin is used only as necessary for therapy of angina. Any incremental effect of reducing the extent of ventricular remodeling by long-term use of long-acting nitrates, if present, is assumed to be uniform within a given patient. No clear effect on infarct remodeling has been shown for diltiazem (the drug prescribed in the small number of patients taking calcium channel antagonists during the study). Only one patient was taking an angiotensin-converting enzyme inhibitor, which could affect the extent of remodeling (5,15); however, this patient was in the group with inferior wall infarction in which no clear changes in chamber volumes were apparent in any patient during the year after infarction. As a whole, it is assumed that if any additional pharmacologic effects were contributed by concomitant medications, the magnitude of their contribution to the serial observations on global left ventricular volumes was small and consistent throughout the study period.

A final issue and the subject of much conjecture is that of the open artery and its impact on the extent of postinfarction left ventricular remodeling (35,42,43). Seventeen of our 18 patients had patent infarct-related coronary arteries documented during coronary angiography at some time during the

course of their initial hospital stay (either immediately or within 5 to 7 days of infarction). For the group with anterior wall infarction, as compared with chamber volumes previously reported using cine computed tomography in normal subjects (26), chamber dilation was apparent at hospital discharge and continued throughout the year after infarction. If the open artery truly limits the extent to which remodeling occurs after infarction, the results of this study have underestimated the magnitude of left ventricular chamber volume and muscle mass changes after transmural infarction that could occur in patients who do not achieve early coronary patency. Whether the open artery observations represent an epiphenomenon or an important pathophysiologic mechanism remains to be completely addressed. However, because we did not have a companion group who had nonpatent infarct-related arteries at hospital discharge, this issue cannot be addressed by the current study design.

The results presented here examine only global left ventricular chamber volumes and muscle mass and do not address the important issues of the dynamic changes in regional volumes. More exacting quantitative analysis is necessary as it pertains to changes in chamber volumes, wall thicknesses (44) and muscle mass on a global and regional basis during the weeks, months and years after an initial transmural myocardial infarction to more fully comprehend the process of postinfarction ventricular remodeling in humans. Work is underway in our laboratory to define infarct size quantitatively by analysis of regional wall thickening rather than use of the approximate methods used in the current investigation. The next planned step is to investigate regional ventricular mechanics after infarction using cine computed tomography in addition to reevaluation of a group of postinfarction patients who are now 2 to 3 years after the index infarction. These data will allow for a much better understanding of the effects of continued postinfarction remodeling on long-term changes in ventricular chamber volumes, muscle mass and global and regional function and will be especially important in the interpretation of studies designed to define the potential salutary effects of the long-term use of angiotensin-converting enzyme inhibitor therapy after infarction.

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